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(71) Applicant *(for all designated States except US)*: **ALCON UNIVERSAL LTD.** [CH/CH]; Bosch 60, P.O. Box 62, CH-6331 Hunenberg (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RUSINKO, Andrew** [US/US]; 2502 Mandy Way, Arlington, TX 76017 (US). **HELLBERG, Mark, R.** [US/US]; 5211 Overridge Drive, Arlington, TX 76017 (US). **NAMIL, Abdelmuola** [FR/US]; 6007 Green Forest Court, Arlington, TX 76001 (US).

(74) Agents: **YEAGER, Sally, S.** et al.; R & D Counsel, 6201 South Freeway, Mail Code Q-148, Fort Worth, TX 76134 (US).

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(54) Title: 2-ACYLAMINOBENZIMIDAZOLE DERIVATIVES FOR TREATING GLAUCOMA

(57) Abstract: 2-Acylaminobenzimidazole deviates useful for treating glaucoma are disclosed.

2-ACYLAMINOBENZIMIDAZOLE DERIVATIVES FOR TREATING GLAUCOMA

The present invention is directed to novel substituted 2-acylaminobenzimidazoles and the use of novel and known 2-acylaminobenzimidazoles for lowering and controlling normal or elevated intraocular pressure (IOP) and treating glaucoma.

Background of the Invention

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated, but no apparent loss of visual function has occurred; such patients are considered to be a high risk for the eventual development of the visual loss associated with glaucoma. Some patients with glaucomatous field loss have relatively low intraocular pressure. These so called normotension or low tension glaucoma patients can also benefit from agents that lower and control IOP. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility. Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

It has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888. Compounds that act as agonists at 5-HT_2 receptors are well known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous system (CNS). U.S. Patent 5,494,928 discloses certain 2-

(indol-1-yl)-ethylamine derivatives that are 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S. Patent 5,571,833 discloses tryptamine derivatives that are 5-HT_2 agonists for the treatment of portal hypertension and migraine. U.S. Patent 5,874,477 discloses a method for treating malaria using 5-$HT_{2A/2C}$ agonists. U.S. Patent 5,902,815 discloses the use of 5-HT_{2A} agonists to prevent adverse effects of NMDA receptor hypo-function. WO98/31354A2 discloses 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. Agonist response at the 5-HT_{2A} receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT_{2C} receptor possible [Psychopharmacology, Vol. 121:357, 1995].

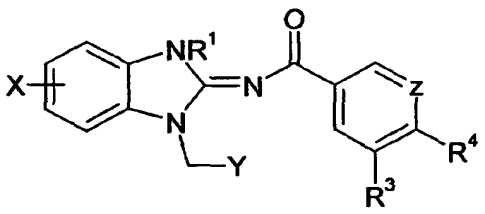
Certain 2-acylamino benzimidazole analogs have been reported [*Chemistry of Heterocyclic Compounds* 33, 293 (1997), *Eur. J. Med. Chem.* 33, 685 (1998)]. No utility has been associated with these compounds.

Summary of the Invention

The present invention is directed to derivatives of 2-acylaminobenzimidazole which can be used to lower and control IOP associated with normal-tension glaucoma, ocular hypertension, and glaucoma in warm blooded animals, including man (Compounds). The compounds are formulated in pharmaceutical compositions suitable for topical delivery to the eye.

Description of the Preferred Embodiments

Compounds that are useful for lowering and controlling normal or elevated intraocular pressure (IOP) and treating glaucoma according to the present invention are represented by the following Formula I.



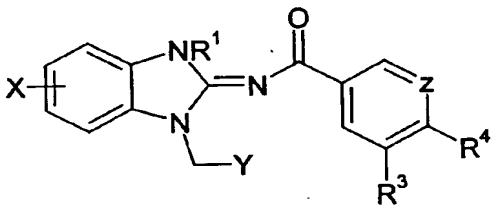
I

Wherein:
X = H, F, Cl, Br, OR^1, CN, $C(=O)R^1$, $C(=O)NR^1R^2$, C_{1-6} alkyl, $OC(=O)R^1$, $OC(=O)NR^1R^2$, or CF_3;
R, R^1, R^2= H or C_{1-6}alkyl;
Y = CH_2NRR^2 or CHR^1NRR^2,
Z = CH or N
R^3 = H, F, Cl, Br, OR^1, CN, C_{1-6} alkyl or CF_3; and
R^4 = H, C_{1-3} alkyl, F, Cl, Br, I or CF_3.

The preferred compounds are those in which: X = H, F, Cl, Br, OR^1, or C_{1-3} alkyl, and R^1 = H, Z= CH.

The most preferred compounds are those wherein: X = H, F, Cl, Br, OR^1, C_{1-3} alkyl, or CF_3; R and R^2 = CH_2CH_3; and R^4 = CH_3 , Z= CH.

Novel compounds are represented by the following Formula I.



I

Wherein:
X = H, F, Cl, Br, OR^1, CN, $C(=O)R^1$, $C(=O)NR^1R^2$, C_{1-6} alkyl, $OC(=O)R^1$, $OC(=O)NR^1R^2$, or CF_3;
R, R^1, R^2= H or C_{1-6}alkyl;
Y = CH_2NRR^2 or CHR^1NRR^2 or with the proviso that when X =H, Y does not equal $CH_2N(CH_2CH_3)_2$;
Z = CH or N
R^3 = H, F, Cl, Br, OR^1, CN, C_{1-6} alkyl or CF_3; and
R^4 = H, C_{1-3} alkyl, F, Cl, Br, I or CF_3.

It is recognized that compounds of Formula I can contain one or more chiral centers. This invention contemplates all enantiomers, diastereomers, and mixtures thereof.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where the numbers i and j define the number of carbon atoms; this definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups.

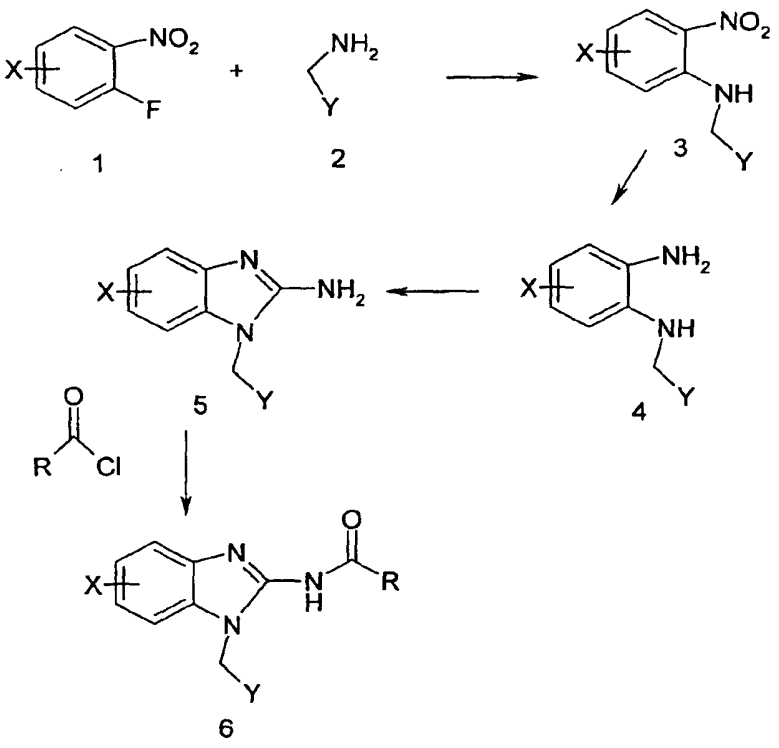
It is important to recognize that a substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine, chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

SYNTHESIS

The desired substituted 2-acylaminobenzimidazoles can be prepared by the method below outlined:

The appropriately substituted 2-nitrofluorobenzene **1** is reacted with the aminoalkylamine derivative **2**. Reduction of the resulting nitroaniline **3** by catalytic hydrogenation (Pd/C, H_2) or by reaction with dithionite yields the diamine **4**. Cyclization with cyanogen bromide leads to the desired 2-aminobenzimidazole **5**. Acylation of the 2-aminobenzimidazole derivative **5** with an acid chloride in the presence of a base such as triethylamine provides the desired 2-acylaminobenzimidazole **6**. The modification of the described synthetic method by the use of certain protecting groups as appropriate can be readily accomplished by one skilled in the art.

Scheme 1



The Compounds of this invention, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but

not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the Compound in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 4 to 8. The Compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.1% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

The compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to, β-blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), α_1 antagonists (e.g. nipradolol), α_2 agonists (e.g., iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travaprost, unoprostone, and compounds set forth in U.S. Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444, "hypotensive lipids" (e.g., lumigan and compounds set forth in 5,352,708), and neuroprotectants (e.g., compounds from U.S. Patent No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S.S.N. 06/203350, and appropriate compounds from WO94/13275, including memantine.

The following methods can be used to characterize Compounds of the present invention. The examples are given to illustrate the preparation of Compounds but should not be construed as implying any limitations to the claims. The preferred Compound of Formula I is described in Example 1.

METHOD 1

5-HT_2 Receptor Binding Assay

In order to determine the relative affinities of serotonergic compounds at the 5-HT_2 receptors, their ability to compete for the binding of the agonist radioligand [^{125}I]DOI to brain 5-HT_2 receptors is determined as described below with minor modification of the literature procedure [Neuropharmacology, 26, 1803 (1987)]. Aliquots of post mortem rat or human cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [^{125}I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1 hour at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analyzed using a non-linear, iterative curve-fitting computer program [Trends Pharmacol. Sci., 16, 413 (1995)] to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [^{125}I]DOI binding by 50% of the maximum is termed the IC_{50} or K_i value.

METHOD 2

5-HT_2 Functional Assay: Phosphoinositide (PI) turnover assay

The relative agonist activity of serotonergic compounds at the 5-HT_2 receptor can be determined in vitro using the ability of the compounds to stimulate the production of [^{3}H]inositol phosphates in [^{3}H]myo-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO_2 and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously [J. Pharmacol. Expt. Ther., 286, 411 (1998)]. Confluent cells are exposed for 24-30 hrs to 1.5 µCi [^{3}H]-myo-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12 containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold

0.1 M formic acid added to stop the reaction. The chromatographic separation of [^{3}H]-inositol phosphates ([^{3}H]-IPs) on an AG-1-X8 column is performed as previously described [J. Pharmacol. Expt. Ther. 286, 411 (1998)] with sequential washes with H_2O and 50 mM ammonium formate, followed by elution of the total [^{3}H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [^{3}H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC_{50} value) and efficacy (E_{max}). Serotonin (5-HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5-HT (set at 100%). The concentration of the compound needed to stimulate the production of [^{3}H]-IPs by 50% of the maximum response is termed the EC_{50} value. Compounds are considered potent agonists if their EC_{50} values in this functional assay are $\leq$ 1 μM and are considered full agonists if their efficacy is > 80% of that of 5-HT.

The above procedures were used to generate the data shown in Table 1.

Table 1. 5-HT2 Receptor Binding and Functional Data.

Compound	IC_{50}, nM	EC_{50}, nM	Efficacy (E_{max}, %)
(R)-DOI	0.46	277	82
Example 1	330	404	35

METHOD 3

Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys

Intraocular pressure (IOP) can be determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes are washed with saline after each measurement. After a baseline IOP measurement, test compound is instilled in one 30 μL aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle is instilled in the right eyes of six additional animals. Subsequent IOP measurements are taken at 1, 3, and 6 hours.

EXAMPLE 1

1-(*N,N*-Dimethylaminoethyl)-2-(4-methylbenzamido)benzimidazole

Step A. 1-(*N,N*-Dimethylaminoethyl)-2-aminobenzimidazole

2-Fluoronitrobenzene (2.00 g, 14.17 mmol) was dissolved in DMF (20 mL) at room temperature, to this solution was added K_2CO_3 (2.93 g, 21.24 mmol) followed by N,N-dimethylethylendiamine (1.87 g, 21.26 mmol). The reaction mixture was stirred overnight, diluted with H_2O (100 mL) and then extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to give an orange oil (4.5 g). ^1H NMR ($CDCl_3$): δ 2.2 (6H, $2CH_3$), 2.51(m, 2H, CH_2), 3.35 (m, 2H, CH_2), 6.64 (m, 1H), 7.01(d, 1H), 7.54 (m, 1H), 7.95 (d, 1H), 8.28(m, NH). This material was dissolved in ethanol (50 mL) and 0.5 g of Pd/C 10 % was added. The mixture was subjected to hydrogenation. Starting material was consumed (TLC) after 2h. Filtration of the catalyst and evaporation of the solvent gave an oily residue (1 g, 5.58 mmol) which was dissolved in CH_2Cl_2 (100 mL). To this solution was added BrCN (2.23 mL of 3M solution in CH_2Cl_2) dropwise at room temperature. The reaction mixture was stirred overnight and the solvent was evaporated. The residue was purified by flash chromatography using methanol-triethylamine (5%) to give 0.5 g of the desired material. MS 204 (m+1). ^{1}HNMR (DMSO): δ 2.22 (s, 6H, $2CH_3$), 2.65(m, CH_2), 4.24 (t, CH_2), 6.66 (s, NH_2) 7.10 (m, 2H), 7.32 (m, 2H).

Analysis for $C_{11}H_{16}N_4$ + 0.2 H_2O. Calculated: C 63.56, H 7.95, N 7.60. Found: C 63.15, H 7.59, N 7.59.

Step B. 1-(*N,N*-Dimethylaminoethyl)-2-(4-methylbenzamido)benzimidazole

1-(*N,N*-Dimethylaminoethyl)-2-aminobenzimidazole (0.40 g, 1.96 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C, triethylamine (2 mL) was added followed by 4-methybenzoyl chloride (0.26 g, 1.96 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for an additional 1h. The volatiles were evaporated and then the residue was purified by column chromatography using CH_2Cl_2-MeOH (9.8-0.2). The oily material collected (0.2 g) was dissolved in anhydrous ethyl ether and transformed to the hydrochloride salt. MS 322 (M+1). ^1H NMR (DMSO): δ 2.48 (s, 3H), 2.81 and 2.86 (2s, 6H), 3.54 (m, 2H), 4.73 (m, 2H), 7.34 (m, 4H), 7.52 (2m, 2H), 8.14 (d, 2H), 10.79 (broad s, NH).

Analysis for $C_{19}H_{22}N_4O$ + 2HCl + 0.3 H_2O. Calculated: C 55.21, H 6.34, N 13.55. Found: C 54.94, H 6.55, N 13.32.

EXAMPLE 2

1-(2-Aminopropyl)-2-(4-methylbenzamido)benzimidazole

Step A. 1-(2-*tert*-Butoxy carbonyl aminopropyl)-2-aminobenzimidazole hydrobromide

1-(2-*tert*-Butoxy carbonyl aminopropyl)-2-aminobenzimidazole hydrobromide was prepared by the method of Example 1 using 2-tert-butoxycarbonyl aminopropylamine and 2-fluoro-nitrobenzene as starting materials. The cyclization reaction using cyanogen bromide gave the desired material as a solid which was collected by filtration MS 290 (M+1). ^{1}H NMR (DMSO): δ 0.74 (s, 9H,) 0.96 (d, 3H), 3.67 (m, 3H), 6.57 (d, 1H), 7.03(m, 3H), 8.44 (s, 2H, NH_2), 12.35 (broad s, NH).

Step B. 1-(2-Aminopropyl)-2-(4-methylbenzamido)benzimidazole

To a solution of 1-(2-*tert*-butoxyaminopropyl)-2-aminobenzimidazole hydrobromide (1.00 g, 2.70 mmol) and triethylamine (1.9 mL, 3.79 mmol) in CH_2Cl_2 (50 mL) was added 4-methylbenzoyl chloride (0.46 g, 29.73 mmol) at 0 ^{0}C. This mixture was stirred at 0 °C for 1 h and at room temperature overnight. The volatiles were evaporated and the residue was purified by flash chromatography using ethyl acetate-hexane (1:1). The fractions collected were concentrated in vacuo and the residue was dissolved in trifluoroacetic acid (5 ml) and stirred overnight. The trifluoroacetic acid was evaporated and the residue was dissolved in ethyl acetate and washed with a saturated solution of bicarbonate. Ethyl acetate was evaporated and the residue was purified by flash chromatography using CH_2Cl_2-MeOH (9.5: 0.5). The oil recovered after evaporation of solvent was transformed to the hydrochloride salt. MS 308 (M+1). ^{1}HNMR (DMSO): δ1.3(d, 3H), 2.37 (s, CH_3), 3.80 (m, 1H), 4.45 (m, 2H), 7.26 (m, 4H), 7.55 and 7.62 (2d, 2H), 8.15 (d, 2H), 11.61 (bs, NH).

Analysis for C_{18} H_{20} N_4O + 2HCl + 0.1 H_2O. Calculated: C 56.43, H 5.84, N 14.62. Found: C 56.26, H 5.77, N 14.50.

EXAMPLE 3

1-(*N,N*-Diethylaminoethyl)-2-(4-methylbenzamid)-6-methoxybenzimidazole

Step A. 1-(*N,N*-Diethylaminoethyl)-2-amino-6-methoxybenzimidazole

1-(*N,N*-Diethylaminoethyl)-2-amino-6-methoxybenzimidazole was prepared by the method of Example 1 using 2-fluoro-4-methoxybenzimidazole and *N,N*-diethylethylenediamine as starting materials. MS 262 (M+1). ^{1}H NMR (DMSO): δ 1.00 (t, 6H, $2CH_3$), 2.55(m, 4H, $2CH_2$), 2.72 (t, CH_2), 3.11 (m, 2H, CH_2), 3.75 (s, 3H, CH_3O), 6.65 (s, 2H, NH_2), 6.14-6.64 (m, 3H).

Step B. 1-(*N,N*-Diethylaminoethyl)-2-(4-methylbenzamido)-6-methoxybenzimidazole

1-(*N,N*-Diethylaminoethyl)-2-(4-methylbenzamido)-6-methoxybenzimidazole was prepared by the method of Example 2 using 1-(*N,N*-diethylaminoethyl)-2-amino-6-methoxybenzimidazole and 4-methylbenzoyl chloride. ^{1}H NMR (DMSO): δ 1.33(t, 6H), 2.51 (s, CH_3 ar), 3.40 (m, 4H), 3.58 (m, 2H), 3.98 (s, 3H), 4.87 (m 2H), 6.99-8.28 (4 m, 7 H), 11.61 (broad s, NH).

Analysis for $C_{22}H_{28}N_4O_2$ + 2HCl + 0.2 H_2O. Calculated: C 53.99, H 7.00, N 11.45. Found: C 54.17, H 7.05, N 11.45.

EXAMPLE 4

1-(*N,N*-Dimethylaminoethyl)-2-benzamidobenzimidazole hydrochloride

1-(*N,N*-Dimethylaminoethyl)-2-benzamidobenzimidazole hydrochloride was prepared by the method of Example 1 using benzoyl chloride and 1-(*N,N*-dimethylaminoethyl)-2-aminobenzimidazole. MS 308 (M+1). ^{1}H NMR (DMSO): δ 2.92 (s, 3H), 2.94 (s, 3H), 3.60 (m, 2H), 4.75 (m, 2H), 7.27-8.33 (m, 9H), 10.81 (broad s, NH).

Analysis for $C_{18}H_{20}N_4O$ + 2HCl + 0.7 H_2O. Calculated: C 54.88, H 5.99, N 14.22. Found: C 54.65, H 6.14, N 14.12.

EXAMPLE 5

1-(*N,N*-Dimethylaminoethyl)-2-(2-thiophenecarboxamido)benzimidazole hydrochloride

1-(*N,N*-Dimethylaminoethyl)-2-aminobenzimidazole hydrochloride was prepared by the method of Example 1 using thiophenecarbonyl chloride and 1-(*N,N*-dimethylaminoethyl)-2-aminobenzimidazole. MS 314 (M + 1). ^{1}H NMR (DMSO): δ 2.95 (s, 3H), 2.97 (s, 3H), 3.57 (m, 2H), 4.70 (m, 2H), 6.08-7.89 (m, 7H), 10.66 (broad s, NH).

Analysis for $C_{16}H_{18}N_4OS$ +2HCl + 0.2 H_2O calculated: C 49.16, H 5.26, N 14.16. Found: C 48.88, H 5.36, N 14.33.

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

EXAMPLE 6

Ingredients	Amount (wt %)
Compound of Example 3	0.1 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 7

Ingredients	Amount (wt %)
Compound of Example 1	0.1 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 8

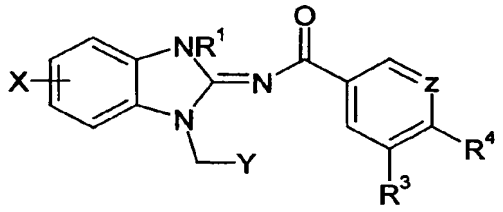
Ingredients	Amount (wt %)
Compound of Example 3	0.1 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 9

Ingredients	Amount (wt %)
Compound of Example 1	0.1 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

We Claim:

1. A compound of the formula:



I

Wherein:

X = H, F, Cl, Br, OR^1, CN, $C(=O)R^1$, $C(=O)NR^1R^2$, C_{1-6} alkyl, $OC(=O)R^1$, $OC(=O)NR^1R^2$, or CF_3;

R, R^1, R^2= H or C_{1-6}alkyl;

Y = CH_2NRR^2 or CHR^1NRR^2 or with the proviso that when X =H, Y does not equal $CH_2N(CH_2CH_3)_2$;

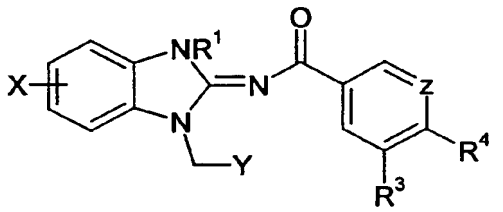
Z = CH or N

R^3 = H, F, Cl, Br, OR^1, CN, C_{1-6} alkyl or CF_3; and

R^4 = H, C_{1-3} alkyl, F, Cl, Br, I or CF_3.

2. The compound of Claim 1 that is 1-(2-aminopropyl)-2-(4-methylbenzamido)benzimidazole.

3. A method for lowering and controlling normal or elevated IOP and treating glaucoma, which comprises administering a pharmaceutically effective amount of a compound of the formula:



Wherein:

X = H, F, Cl, Br, OR^1, CN, $C(=O)R^1$, $C(=O)NR^1R^2$, C_{1-6} alkyl, $OC(=O)R^1$, $OC(=O)NR^1R^2$, or CF_3;

R, R^1, R^2= H or C_{1-6}alkyl;
Y = CH_2NRR^2 or CHR^1NRR^2,
Z = CH or N
R^3 = H, F, Cl, Br, OR^1, CN, C_{1-6} alkyl or CF_3; and
R^4 = H, C_{1-3} alkyl, F, Cl, Br, I or CF_3.

4. The method of Claim 3 wherein the compound is defined as: X = H, F, Cl, Br, OR^1, or C_{1-3} alkyl, and R^1 = H, Z= CH.

5. The method of Claim 3 wherein the compound is defined as: X = H, F, Cl, Br, OR^1, C_{1-3} alkyl, or CF_3; R and R^2 = CH_2CH_3; and R^4 = CH_3 , Z= CH.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/31260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/30 A61K31/4184 A61P27/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SUGRUE M F: "NEW APPROACHES TO ANTIGLAUCOMA THERAPY" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 40, no. 18, 29 August 1997 (1997-08-29), pages 2793-2809, XP000878913 ISSN: 0022-2623 the whole document --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2001	05. 03. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 00/31260

C.(Continuation) DOCUMENTS CONSIDERED T BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DA SETTIMO, ANTONIO ET AL: "Synthesis, DNA binding and in vitro antiproliferative activity of purinoquinazoline, pyridopyrimidopurine and pyridopyrimidobenzimidazole derivatives as potential antitumor agents" EUR. J. MED. CHEM. (1998), 33(9), 685-696, XP004140823 cited in the application see compound 8c page 694	1,2
A	DATABASE CHEMCATS 'Online! AN: 2000:926541 ; Catalog Name: Ambinter: Screening Collection, 23 August 1999 (1999-08-23) XP002160021 Benzamide,N-'1-'2-(diethylamino)ethyl!-1H-benzimidazol-2-yl!-3-fluoro- CAS Registry No.: 296799-22-9	1,2
P,A	DATABASE CHEMCATS 'Online! AN: 2000:930567; Catalog Name: ChemDiv, Inc. Product Library, 7 July 2000 (2000-07-07) XP002160020 Benzamide,N-'1-'2-(diethylamino)ethyl!-1H-benzimidazol-2-yl!- CAS Registry No.: 92613-13-9	1,2

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/US 00/31260

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.